STUDIES ON THE RELATIONSHIP BETWEEN OPTICAL ACTIVITY AND PHYSIOLOGICAL ACTIVITY.

The Synthesis of Compounds Related to Tropic Acid.

by

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It has long been known that, when a physiologically active substance contains an asymmetric carbon atom, the pharmacological effects of the two enantiomorphs, while qualitatively identical, may differ considerably in magnitude. The best illustrations of this phenomenon are given by the substances hyoscyamine, hyoscine and adrenaline, all of which were investigated by Cushny, the pioneer worker in this field. Thus, according to this author, who has summarised his work in his monograph "Biological Relations of Optically Isomeric Substances", the activity of l-hyoscyamine is about twenty times that of its d-isomeride, l-hyoscine is 16-18 times as active as the d-form, while l-adrenaline possesses an activity which is 12-15 times as strong as that of d-adrenaline.

In view of the fact that the physical and chemical properties of optical isomerides are, apart from their behaviour towards polarised light, identical, much work has been carried out with the object of elucidating the cause of their ability to evoke quantitatively different pharmacological effects/

and the latter insipid - to the presence in the nervous mechanism of taste of an optically active substance. King (J. Chem. Soc., 1924, 125, 41), on the other hand, basing his view on the observations of Porter and Ihrig (J. Amer. Chem. Soc., 1923, 45, 1990) that wool, when treated with a solution of racemic m-azo-β-naphthol mandelic acid, selectively removes the dextro form, attributes the different pharmacological effects of optical isomerides in general to the removal from the body fluids of the less active isomeride by optically active constituents of the tissue. Gottlieb (Arch. exp. Path. Pharm., 1923, 97, 113), however, as a special explanation of the different behaviours of d- and l-cocaine, postulates that the former is destroyed more rapidly than the latter by body enzymes.

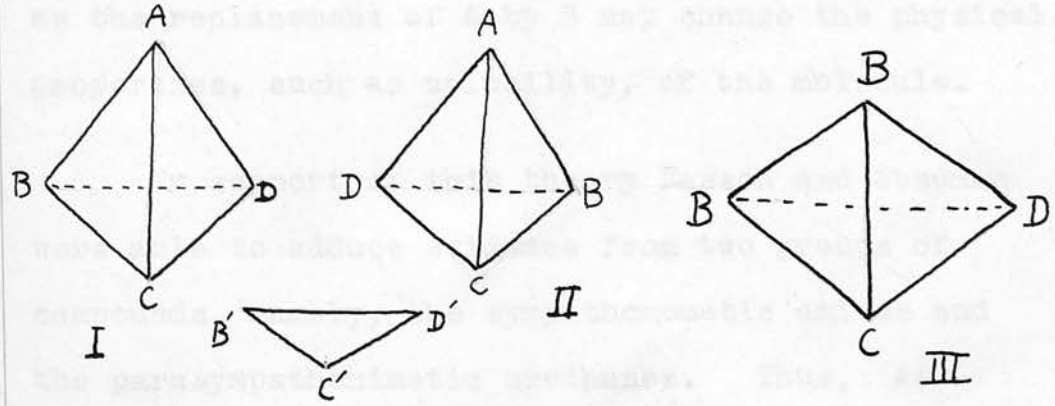
Cushny examined all of these theories in detail, adduced cogent evidence for the rejection of them all as complete and general explanations of the phenomenon under discussion, and came to the conclusion that the effect of optical activity "is almost certainly due to a chemical combination being formed between receptor and drug." He states, in fact, in illustration of his views that "it/

"it may be supposed that l-adrenaline may cause a precipitate readily in the myoneural junction, while d-adrenaline does so only when it is present in much higher concentration, just as they differ in their reaction with camphor-sulphonic acid".

In the work discussed above it has been tacitly assumed by most authors, and explicitly stated by Cushny, that molecular asymmetry with its associated optical activity is, of itself, of influence in the intensification of the pharmacological activity of a molecule. Recently, however, a new theory has been advanced by Easson and Stedman (Biochem. J. 1933, 27, 1257) in which these features are regarded merely as accidental accompaniments of the actual factor which is the true cause of the different biological effects frequently exhibited by antimeric compounds. Easson and Stedman, in fact, are of the opinion that the different pharmacological activities of enantiomorph are caused by precisely the same features as are responsible for the different physiological effects of different symmetrical substances. Their theory postulates(1) that a drug, in order to exert its effect, must combine with/

with a specific receptor in the tissues. It is, of course, recognised that some drugs, e.g. general anaesthetics, may not act in this way, and the theory does not apply to such substances; (2) that it is attached to the receptor at ~~the~~ at least three points.

Upon the basis of these postulates the theory may be best explained by representing asymmetric molecules by tetrahedra in the conventional manner. Thus, let us suppose that the two enantiomorphs of a physiologically active substance are represented by I and II, the former being the more active form. Suppose, further, that the receptor with which they

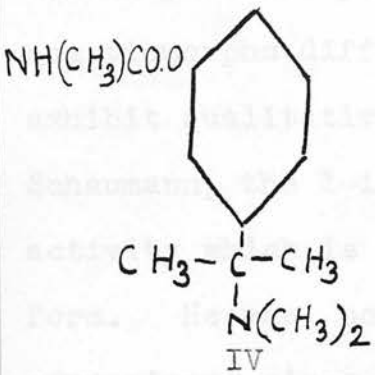


must combine is represented by B'C'D' which must be considered as situated in the surface of the tissue. Now, according to the theory, the best combination between the drug and its receptor will result when the groups BCD in the drug become coincident with the/

the points B'C'D' of the receptor. This can only happen in the case of I; hence the greater activity of this isomeride. Now let us suppose that the group A in I has been replaced by a second group B. The resulting molecule is represented by III. It is at once clear from the diagram that the base of III can be brought into coincidence with the receptor in exactly the same way as that of I despite the fact that the introduction of a second group B into the molecule has destroyed its asymmetry. According to this theory III should possess a physiological activity which is quantitatively identical with that of I except in so far as the replacement of A by B may change the physical properties, such as solubility, of the molecule.

In support of this theory Easson and Stedman were able to adduce evidence from two groups of compounds, namely, the sympathomometic amines and the parasympathomimetic urethanes. Thus, as predicted by the theory, 3:4-dihydroxy-β-phenylethylmethylamine was calculated from measurements recorded in the literature to possess a pressor activity which was, within the limits of experimental error, identical with that of d-adrenaline. Similarly, the methylurethane of α-m-hydroxyphenyl-

isopropyldimethylamine (IV) proved to be more active than d- and only slightly less active than



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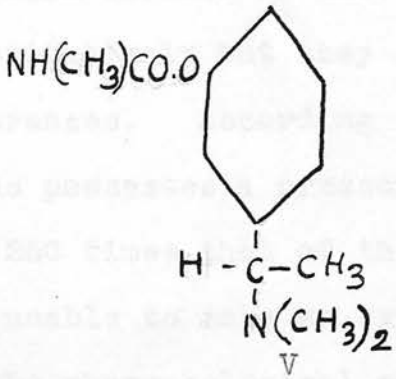
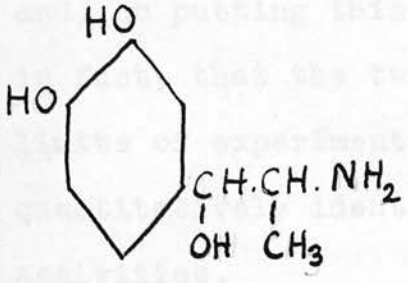
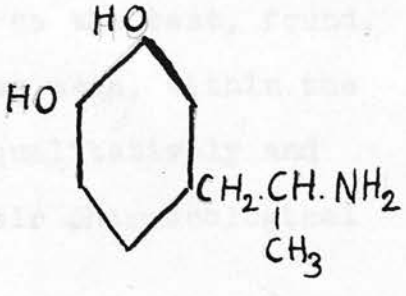


V

l-miotine (V). More recently Schaumann (Reports from the Medico-Chemical Research Laboratories of the I.G. Farbenindustrie Aktiengesellschaft, 1938, vol. III) has examined d- and l-corbasil (3:4-dihydroxy-nor-ephedrine; VI) and has obtained results



VI



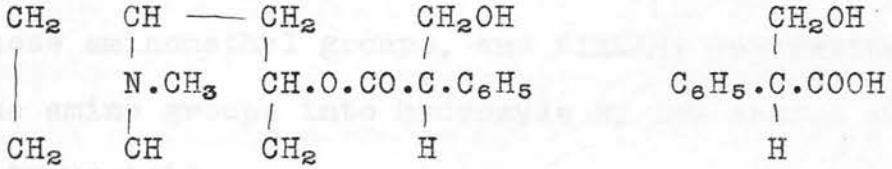
VII

which he regards as offering a confirmation of Easson and Stedman's theory. Corbasil does, in fact, afford a crucial test of the theory, since not/

not only do the physiological effects of the enantiomorphs differ quantitatively but they also exhibit qualitative differences. According to Schaumann, the l-isomeride possesses a pressor activity which is 160 to 250 times that of the d-form. He was, however, unable to make an exact comparison, since while the pharmacological action of l-corbasil resembles that of adrenaline, the d-isomeride behaves like ephedrine. On the basis of Easson and Stedman's theory Schaumann deduced that α-3:4-dihydroxyphenylisopropylamine should resemble d-corbasil in its physiological effects and, on putting this deduction to the test, found, in fact, that the two substances were, within the limits of experimental error, qualitatively and quantitatively identical in their pharmacological activities.

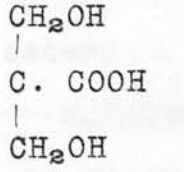
The present investigation was commenced with the object of providing further evidence by which the theory discussed above could be judged, and in view of the marked differences between the pharmacological activities of d- and l-hyoscyamine, this substance was chosen for study. Hyoscyamine(VIII) is/

is the tropyl ester of tropic acid (IX), the



VIII IX

optical activity of the alkaloid being due to the asymmetric carbon atom present in the tropic acid moiety of the molecule. Now, Cushny has produced convincing evidence to show that the presence of the alcoholic hydroxy group in the acidic portion of the protein is essential for marked physiological activity . In order to retain this group while destroying the asymmetry of the molecule it would be necessary to prepare phenyldihydroxymethyl acetic acid (X). Two general methods by which this object



X.

might/

might be achieved appeared to be available:

(1) By the introduction of cyano groups into the methylene group of phenylacetic acid, reducing these aminomethyl groups, and finally converting the amino groups into hydroxyls by the action of nitrous acid.

(2) By the direct introduction of an hydroxymethyl group into the tropic acid molecule.

The possibility of using a combination of these two methods has also been examined.

As the introduction of cyano groups appeared to offer the best prospects of success, this method was first investigated. The starting material in this case was phenylcyanoacetic ester. This was converted by Hessler's method (J. Amer. Chem. J. 1910, 32, 120) through the amide into phenyl malononitrile. The latter reacted readily with metallic sodium and the sodium salt, when treated with chloroformic ester yielded the required phenyldicyanoacetic ester:

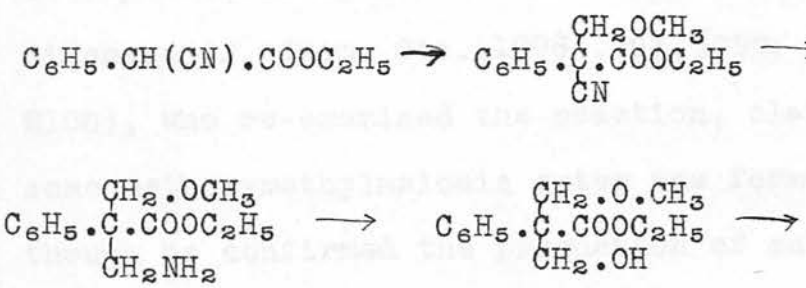
$C_6H_5.CH(CN).COOC_2H_5 \rightarrow C_6H5.CH(CN).CO.NH_2 \rightarrow C_6H_5.CH(CN)_2 \rightarrow C_6H_5.CNa(CN)_2 \rightarrow C_6H_5.C(CN)_2.COOC_2H_5$.

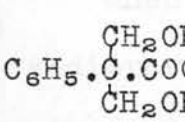
Unfortunately, however, all attempts to reduce this substance/

substance proved fruitless.

A combination of the above two general methods was therefore attempted. For the introduction of an hydroxymethyl group into the molecule, chloromethylmethyl ether was first utilised with a view to the preparation of the methyl ether of the required alcohol which could then be demethylated with hydrobromic acid.

Starting again from phenylcyanoacetic ester, the scheme in view can be represented as follows:-





Chloromethylmethyl ether has not hitherto received much attention with respect to reactions of this nature. A search of the literature, however, revealed the fact that Kleber (Annalen, 1888, 246, 97) examined its behaviour towards sodiomalonic ester and found that it reacted in

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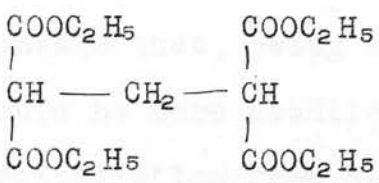
a somewhat complex manner, the products being



XI.

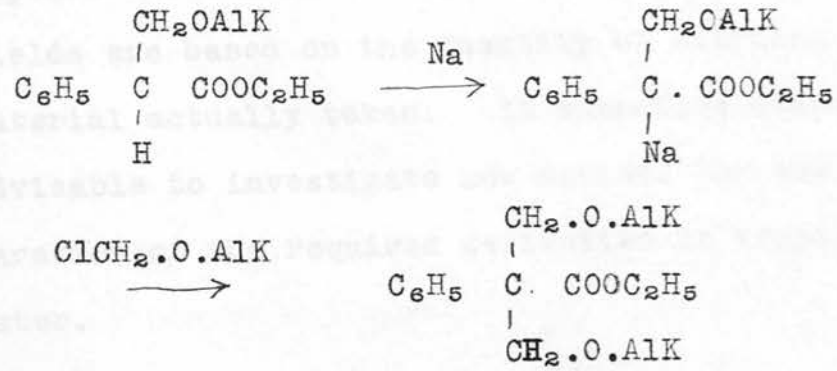
dimethoxymethyl malonic ester and a substance which he represented by formula XI. On the other hand, Simonsen (J. Chem. Soc.,1908 , 93, 1777; 1909 , 95, 2106), who re-examined the reaction, claimed that some methoxymethylmalonic ester was formed, although he confirmed the production of substance XI.

When the ether was added to a suspension of sodiophenylcyanoacetic ester interaction occurred almost instantaneously and the product was found to contain the required phenylmethoxymethylcyanoacetic ester. It was, however, admixed with unchanged phenylcyanoacetic ester and, owing to the small difference between the boiling points of the two liquids, separation could only be effected by a long and tedious process of fractional distillation. In order to facilitate separation from unchanged material it was therefore decided to use chloro-

methyl-/

methylethylether in place of the chloromethylmethyl-ether. The use of the former ether possessed the further advantage that, owing to its higher boiling point, it could be more readily separated by fractional distillation from hydrochloric acid, with a resulting greater yield of product. The phenyl-methoxymethylcyano acetic ester so obtained proved, however, to be as resistant to the action of reducing agents as the phenyldicyanoacetic ester mentioned above. Attempts at catalytic reduction, using Adam's platinum oxide catalyst failed completely, no measurable amount of hydrogen being absorbed. Aluminium amalgam was also ineffective as also was the process of electrolytic reduction. At the suggestion of Dr W. Robson, an attempt was made to reduce the cyano group with hydrogen sulphide by the process which Harvey and Robson (J. Chem. Soc. 1938, p. 100) had found so successful in the hydro-genation of difficultly reducible double bonds, but no trace of basic material was produced.

In view of the fact that the first general method outlined above did not lead to the desired result the second method was investigated. This, it will be recalled, visualised the introduction of hydroxymethyl groups into the phenylacetic acid molecule. Had tropic acid itself, which contains one such group, been a readily accessible substance, this problem would not have appeared to present much difficulty. After methylation of tropic ester to protect the hydroxyl group, it was anticipated that the resulting ether would react readily with sodium, thus enabling a second alkoxymethyl to be introduced into the molecule:



Unfortunately, however, no very satisfactory method for the preparation of tropic acid is known. Several methods have, it is true, been recorded, but, according to McKenzie and Wood (J. Chem. Soc., 1919, 115, 828) all of these are, with the exception of

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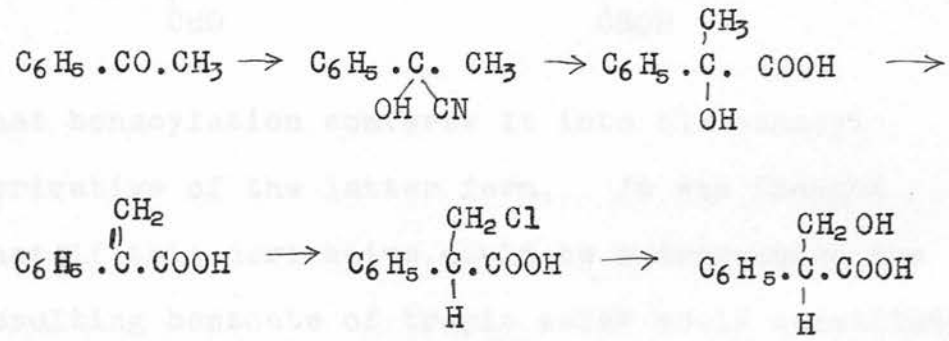
the one which they themselves describe, virtually unworkable. And even their own method, which takes the following course,



while giving yields at each stage which are reasonable when based on the proportion of starting material which has entered into the reaction, appears to be much less satisfactory when the yields are based on the quantity of starting material actually taken. It therefore seemed advisable to investigate new methods for the preparation of the required derivative of tropic ester.

A variety of methods appeared to be available for this purpose. Wislicenus (Annalen, 1896, 291, 164) has shown that phenylformylacetic ester, as prepared by the interaction of phenylacetic and formic/

formic esters in the presence of metallic sodium, is a mixture of two tautomeric forms:

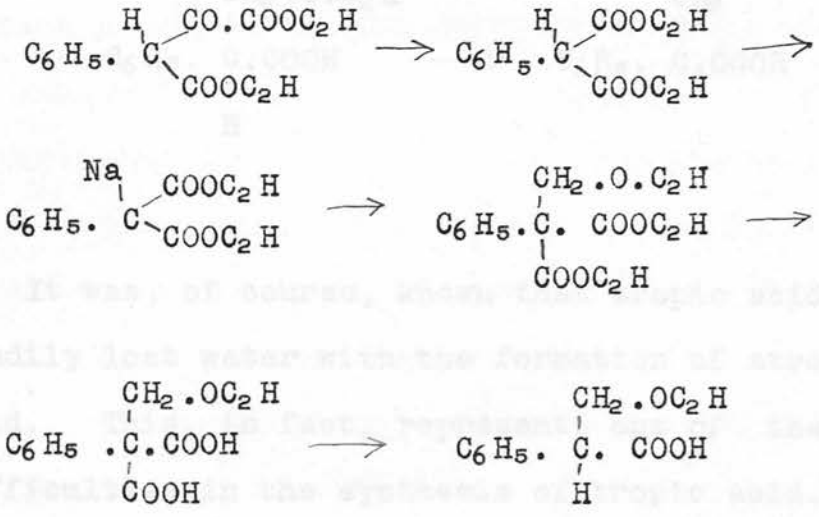
$C_6H_5.CH(CHO).COOEt$ and $C_6H_5.C(CHOH).COOEt$ and

that benzoylation converts it into the benzoyl derivative of the latter form. It was thought that if this derivative could be hydrogenated the resulting benzoate of tropic ester would constitute a suitable substance with which to carry out the remaining stages of the synthesis. Müller (Ber., 1918, 51, 252) had, it is true, failed in his attempts to effect its reduction, but it was thought that better results might be obtained with the improved catalysts now available. Absorption of hydrogen was, however, exceedingly slow and could only be accounted for by the reduction of the benzene ring itself. There was a possibility that the resistance which this compound offered to reduction was due to the accumulation of negative groups in the molecule. By means of a method for the alkylation of hydroxymethylene compounds due to Claisen but only recently described by v. Auwers (Ber., 1938, 71, 2082) the ethyl ether of/

of the hydroxymethylene form of phenylformylacetic ester was therefore prepared. Its behaviour towards catalytic reduction, however, was entirely similar to that of the benzoyl derivative. It seems very probable that the reduction of compounds of this type could be effected by the method, mentioned above, which has recently been described by Harvey and Robson for use in connection with the reduction of double bonds which can only otherwise be hydrogenated with great difficulty. This reaction, however, has not been examined in this case since the desired ether of tropic ester has been prepared by another route.

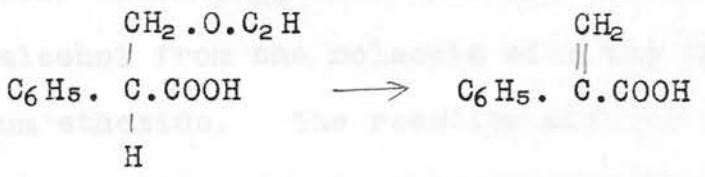
After examining certain other methods, which are described in the experimental portion, for the preparation of the ethylether of tropic ester the following procedure was adopted. Phenyloxalylacetic ester, prepared according to Wislicenus' method (Ber., 1894, 27, 1091; Annalen, 1888,246,315[2]) was converted by distillation into phenylmalonic ester. This readily formed with powdered sodium sodio/

sodiophenylmalonic ester which reacted smoothly. with chloromethylethyl ether to yield phenylethoxy methyl malonic ester. Hydrolysis of the latter gave the free dicarboxylic acid, which readily lost carbon dioxide to give the ethyl ether of tropic ester. The reactions involved can be represented as follows:



Considerable difficulty was, however, at first experienced in the hydrolysis of ethoxymethylphenyl malonic ester. Even under the mildest conditions the product consisted of a mixture of substances. Not only was ethoxymethylphenylmalonic acid present, but some of this had lost carbon dioxide with the formation of ethoxymethylphenylacetic acid (tropic acid/

acid ethyl ether). The chief difficulty encountered was, however, due to the fact that even under the mild conditions of hydrolysis employed a certain proportion of atropic acid was always found in the reaction product. This was presumably produced by loss of ethyl alcohol from the ethyl ether of tropic acid as follows:-



It was, of course, known that tropic acid itself readily lost water with the formation of atropic acid. This, in fact, represents one of the difficulties in the synthesis of tropic acid. But it had been anticipated that this reaction would have been entirely suppressed when the hydroxyl group was protected by ethylation. Nevertheless, it was found possible, as will be described in the experimental portion, to obtain by the above method reasonably good yields of the ethyl ether of tropic acid and this could be converted quantitatively into its ester.

With/

With the synthesis of this ester it was now possible to attempt to introduce a second ethoxymethyl group into the molecule. The ethyl ether of tropic ester reacted smoothly with powdered sodium with the evolution of hydrogen. The solution, however, became somewhat brown in colour and no precipitate of the required sodium salt was produced, a behaviour which suggested that the sodium was removing alcohol from the molecule with the formation of sodium ethoxide. The reaction mixture was, nevertheless, treated with chloromethylethyl ether, when a brisk reaction occurred. The product, however, proved to be a thick oil, part of which boiled at a constant temperature. Analysis of this fraction indicated a composition which suggested that the net effect of the sodium was to remove one molecule of ethyl alcohol from two molecules of the ethyl ether of tropic ester, the product being, no doubt, a mixture of condensation products of high molecular weight. This behaviour was reminiscent of that of phenylacetic ester under the influence of sodium in some experiments in which an attempt was made to introduce an ethoxymethyl group directly into the phenylacetic ester molecule.

The experiments carried out seem to make it clear that, when one of the hydrogen atoms of the methylene group in phenylacetic ester has been replaced by a cyano group, it is then possible to replace the second hydrogen with sodium with the formation of a stable sodium derivative; this will then react with alkyl halides in the normal manner. When on the other hand, neither hydrogen is so replaced, or when one is replaced by an alkoxyalkyl group, no stable sodium derivative is formed. On the contrary, metallic sodium causes a condensation, the exact nature of which is unknown, to occur between two or more molecules of the ester. It is thus evident that neither of the two general methods outlined above will lead to the preparation of dihydroxymethylphenylacetic acid and the realisation of the synthesis of this substance must await the development of a new method of attack.

In addition to the experiments enumerated above some subsidiary methods of attack were examined, although these also proved to be unsuccessful. Thus, inview of the failure to reduce phenylethoxymethylcyanoacetic ester some experiments were carried out to ascertain if the cyano group could

be converted into an aldehyde group, which might then undergo reduction, bythe method introduced by Stephen (J. Chem. Soc., 1925, 127, 1874) a few years ago. This method depends on the conversion of the cyano compound into the imino-chloride which is then reduced by anhydrous stannous chloride to the aldimine, the stannichloride of which separates in crystalline form. Hydrolysis of the aldimine yields the aldehyde:-

$$R.CN + HCl \longrightarrow R.CCl{:}NH; \quad R.CCl{:}NH + SnCl_2 + 2HCl \longrightarrow$$

$$R.CH{:}NH, HCl + SnCl_4 \qquad R.CH{:}NH + H_2O \longrightarrow R.CHO + NH_3$$

When applied to benzonitrile this method worked exactly as described by Stephen. With phenyl-ethoxymethylcyanoacetic ester, on the other hand, only in appreciable amounts of stannichloride were formed. Nor could any better result be achieved when the modifications of the method, suggested by King and Robinson (J. Chem. Soc., 1933, 272) and King (J. Chem. Soc., 1936, 35) for use with sluggishly reacting cyanides, were tried.

Before the ethyl ether of tropic ester had been prepared by the method already outlined some/

some attempts had been made to obtain it by the hydrolysis of phenylmethoxymethylcyanoacetic ester. When direct hydrolysis was used, some decarboxylation, as indicated by the evolution of carbon dioxide, always occurred. As a result the product was not homogeneous and could not be purified.

Nor could the corresponding amide be obtained by the action of concentrated sulphuric acid on the cyano compound, although this method readily converted phenylcyanoacetic ester into the amide in practically quantitative yield.

E X P E R I M E N T A L.

Preparation of phenyldicyanoacetic ester, $C_6H_5.C(CN)_2.COOC_2H_5$.

Phenylcyanoacetic ester. The phenylcyanoacetic ester used in these experiments was prepared partly by Hessler's method (J. Amer. Chem. Soc., 1910, 32, 120) and partly by that of Bodroux (Comptes rend., 1910, 151, 1358). In the former method, 11 g. of sodium were pressed into wire into a round bottomed flask and covered with 300 c.c. of ether previously dried over sodium. The flask was then fitted with a condenser and dropping funnel and cooled in ice water when 36 g. of diethylcarbonate were added to it. Benzylcyanide (56 g.) was then added drop by drop to the mixture, the vigour of the reaction being regulated by the rate of addition of the benzyl cyanide. After standing overnight the yellow solid which had formed in the reaction mixture was decomposed with dilute sulphuric acid, when the ethereal layer was separated, washed with water, and dried over sodium sulphate. Fractional distillation under diminished pressure of the residue obtained on evaporation of the ether finally gave 32 g. of phenylcyanoacetic ester, b.p. 162-163°/17-18 mm.

In/

In Bodroux's method sodamide is used in place of metallic sodium. The sodamide (11 g.) was crushed under benzene in a mortar. It went partly into solution. Hence the whole contents of the mortar were washed with more benzene into the reaction flask. The remainder of the preparation was then carried out as in Hessler's method. Using 30 g. of benzylcyanide and 33 g. of ethyl carbonate, a yield of 29 g., b.p. 145-147°/ 10 mm., was obtained.

Phenylcyanoacetamide. (Hessler, loc. cit.) Phenylcyanoacetic ester (40 g.) and 0.88 ammonia (49 g.) were mixed together. The mixture became reddish-brown in colour and solidified after 12 hours. Water was added and the solid filtered and washed with more water. On removing the ammonia from the filtrate and washings, a further quantity of solid separated. This was collected, united with the first crop, and the whole crystallised from alcohol, when it melted at 147°.

Phenylmalononitrile. Phenylcyanoacetamide (20 g.) was mixed in an Anchütz flask with about 12 g. of phosphorus pentoxide, and the mixture heated at

120/

120-125° under diminished pressure. When the contents of the flask were in a fused state the temperature of the bath was raised until the phenylmalononitrile distilled into the side tube, where it solidified. Yield of crude material: 10 g. It was recrystallised from dilute alcohol and melted at 68-69°.

A similar yield was obtained when phosphorus pentachloride was used in place of the pentoxide, as recommended by Hessler (loc. cit.)

An attempt to use thionyl chloride in place of phosphorus pentoxide was not successful.

Phenyldicyanoacetic ester. 1.2 g. of metallic sodium were brought into powder form by shaking in a round bottom flask with boiling xylene. The solvent was removed by decantation and, after washing with dry ether, the powder was covered with 50 c.c. of the same solvent. Phenylmalononitrile (7 g.) dissolved in 20 c.c. of ether was then added. After the evolution of hydrogen had ceased, a few c.c. of absolute alcohol were added to remove a small amount of unchanged sodium. The flask was then cooled in ice-water and 10 g. of chloroformic/

chloroformic ester in 10 c.c. of ether were slowly added to the mixture. A vigorous reaction took place, with the separation of sodium chloride. The contents of the flask were then refluxed for an hour, after which water was added to dissolve the sodium chloride and the ethereal layer separated and washed. The extract was dried with sodium sulphate, the ether removed by distillation, and the oily residue stored in a desiccator. After two days it had largely crystallised. It was then dried on a porous plate and recrystallised from benzene by the slow addition of petroleum ether, when it melted at 54.5-55.5°. Yield of pure substance: 3 g.

Analysis:

4.376 mg. gave 10.820 mg. CO_2 and 1.693 mg. H_2O

4.507 mg. gave 0.490 c.c. N_2 at 762/11°.

Found: C = 67.42%; H = 4.33%; N = 13.11.

Calculated for $C_{12}H_{10}O_2N_2$:

C = 67.34%; H = 4.68%; N = 13.09.

attempted/

Attempted hydrogenation of phenyldicyanoacetic ester.

In an attempt to reduce phenyldicyanoacetic ester catalytically, 1 g. of the pure ester was dissolved in alcohol and shaken for some hours in a hydrogen atmosphere with 50 mg. of Adam's platinum oxide catalyst. The absorption of hydrogen was followed by means of a burette attached to the reaction flask. After about an hour, the absorption came practically to a standstill, only about 20 c.c. of hydrogen, mainly required for the reduction of the catalyst, having been absorbed. A similar result was obtained when glacial acetic acid was used as solvent.

Hydrolysis of phenyldicyanoacetic ester.

With a view to obtaining the free acid, one gram of the above ester was dissolved in a small volume of methyl alcohol and, to the solution so obtained 1 g. of potassium hydroxide in 10 c.c. of water was added. The mixture was kept, with frequent shaking, at room temperature for 24 hours. The alcohol was then evaporated and the solution extracted with ether. On acidification of the aqueous/

aqueous layer a brisk effervescence, due to the liberation of carbon dioxide, occurred. The acid solution was, nevertheless, extracted with ether, but no residue was obtained on evaporation of the solvent. After removal of the solvent from the extract from alkaline solution the residue crystallised and proved to be phenylmalononitrile. Evidently the free acid is unstable and readily loses carbon dioxide.

Preparation of phenylmethoxymethylcyanoacetic ester

$$C_6H_5.\ \begin{matrix} CH_2.O.CH_3 \\ | \\ C.COOC_2H_5 \\ | \\ CN \end{matrix}$$

and phenylethoxylmethylcyanoacetic ester,

$$C_6H_5.\ \begin{matrix} CH_2.O.C_2H_5 \\ | \\ C.COOC_2H_5 \\ | \\ CN \end{matrix}$$

Preparation of chloromethylethylether. Chloromethylmethyl ether is a commercial product. It was necessary, however, to prepare chloromethylethyl ether, which was effected by Karvonen's method (Annales Acad. Scient. Fennicae, 1913, Series A, 3, 42). Trioxymethylene (120 g.) and absolute alcohol (200 g.) were mixed in a round bottom flask/

and shaken until they formed a paste. The flask was then fitted with a ground stopper carrying two glass tubes, one of which reached the bottom of the flask, and immersed up to its neck in cold water. The inlet tube was attached to a Kipp apparatus for generating dry hydrogen chloride and the outlet tube to a wash bottle containing mercury, the object of which was to maintain the gas in the apparatus at a pressure slightly greater than that of the atmosphere and hence to facilitate both the reaction and to prevent the escape of hydrogen chloride. Hydrogen chloride was then passed through the mixture until the whole of the trioxymethylene had gone into solution and two liquid layers had separated in the flask, an operation which required about 48 hours for its competion. The upper layer was then separated and left in contact with anhydrous calcium chloride for 7 days. It was then fractionally distilled through a 24" column, glass connections being, as far as possible, used in assembling the apparatus. Where this was not possible, charred corks were employed. Direct contact with the moist atmosphere was prevented by the use of calcium chloride tubes. Arrangements were also made to introduce a slight draught into/

into the apparatus from a water pump in order to carry away the free hydrogen chloride in the liquid. Five such fractionations were actually carried out, the boiling points of the main fractions being recorded below.

First distillation,	b.p.	81-86°
Second	"	"	82-85°
Third	"	"	82.5-84°
Fourth	"	"	83°
Fifth	"	"	83°

The substance thus purified was practically free from hydrogen chloride and did not fume on contact for a short time with the moist atmosphere.

Preparation of chloromethylpropyl ether. This was effected exactly as described above for the corresponding ethyl ether, except that the trioxymethylene was mixed with n-propyl alcohol in place of ethyl alcohol. Only three fractionations of the final product were, in this case, necessary. The chloromethylpropyl ether boiled at 108.5-109°.

Preparation/

Preparation of phenylmethoxymethylcyanoacetic ester.

Sodium (5.3 g.) was powdered in the usual manner in a round-bottom flask, washed by decantation with dry ether, and covered with 150 c.c. of the same solvent. The flask was then fitted with a condenser and dropping funnel and 45 g. of ethylphenylcyanoacetate were added drop by drop. Hydrogen was evolved and a white solid separated. When the reaction had subsided the reaction mixture was heated on a water bath for an hour. It was then cooled in ice water and 25 g. of chloromethylmethyl ether dissolved in an equal volume of dry ether slowly added. A vigorous reaction took place. When the addition was complete the mixture was again refluxed for an hour. The contents of the flask were then acid to litmus, and a precipitate of sodium chloride had formed. This was dissolved by the addition of water, when the ethereal layer was separated and washed with water. After drying over sodium sulphate the ether was removed by distillation and the residual oil fractionally distilled under diminished pressure. After

repeated/

repeated fractionation, 7 g. of material, b.p. 173-175°/16-17 mm. were obtained. This proved to be pure ethylphenylmethoxymethylcyanoacetate.

Analysis:

7.904 mg. gave 19.395 mg. CO_2 and 4.602 mg. H_2O

4.950 mg. gave 0.262 c.c. N_2 at 739 mm. and 15°C.

Found: C = 66.92; H = 6.52; N = 6.10%

$C_{13}H_{15}O_3N$ requires C = 66.95; H = 6.44; N = 6.09%

Preparation of phenylethoxymethylcyanoacetic ester.

The bad yield of ethyl phenylmethoxymethylcyanoacetate obtained in the preceding experiment was due to two causes: (1) the presence of some free hydrochloric acid in the commercial chloromethylmethyl ether employed in the reaction, and (2) the small difference (about 10°) between the boiling points of the product and the starting material, which rendered isolation of the product by fractional distillation an exceedingly wasteful process. It was anticipated that by replacing chloromethylmethyl ether by chloromethylethyl ether a product would be obtained with a higher boiling point and that this would consequently be/

be isolated with greater facility from the reaction product. Chloromethylethyl ether, virtually free from hydrochloric acid, was therefore prepared as described in a preceding section and was made to react with ethylsodiophenylcyanoacetate exactly as described in the preceding experiment. The product was fractionally distilled under diminished pressure, and, after three fractionations, ethylphenylethoxymethylcyano acetate was obtained in a 50% yield boiling at 182-183°/18-19 mm. or at 168-169°/10 mm.

Analysis:

5.248 mg. gave 13.130 mg. CO_2 and 3.320 mg. H_2O

Found: C = 68.22; H = 7.07%

$C_{14}H_{17}O_3N$ requires C = 68.02; H = 6.89%

Preparation of phenylpropoxymethylcyanoacetic ester. This was effected exactly as in the case of its two lower homologues described in the preceding experiments. The crude product distilled between 172° and 192°/20 mm. No attempt was made to purify it by fractional distillation, but the material was used to determine if esters of this nature could be separated from unchanged phenylcyanoacetic ester by chemical means. The crude

oil/

oil (34 g.) was added slowly to 1.7 g. of powdered sodium under 150 c.c. of dry ether. The solution became dark brown in colour, but little precipitate was formed. It had been hoped that the unchanged phenylcyanoacetic ester would form with the sodium an insoluble sodium derivative which could be filtered from the solution leaving an ethereal solution of relatively pure propoxymethyl derivative. As this did not happen an attempt was made to recover the material. The solution was filtered, washed with water and dried over sodium sulphate. The oil left on evaporation of the ether proved to be very viscous and would not distil. Evidently, under the influence of sodium, a reaction had occurred between the unchanged ester and its propoxymethyl derivative. It was clear that this method could not be used to facilitate the isolation of the compounds under investigation.

Attempted reduction of phenylmethoxymethylcyanoacetic ester. Two grams of the ester were dissolved in 10 c.c. of glacial acetic acid and introduced into the bulb of the hydrogenation apparatus/

apparatus. 0.1 g. of Adam's platinum oxide catalyst was then added, the bulb evacuated, washed out three times with hydrogen and finally filled with this gas at atmospheric pressure. The apparatus was then shaken until the catalyst was reduced. At this point 10 c.c. of glacial acetic acid saturated with dry hydrogen chloride were introduced into the bulb, this addition being made because, according to Kindler (Annalen, 1931, 485, 113), a high concentration of hydrochloric acid represses the formation of secondary amines when cyanides are reduced. The apparatus was then shaken for 72 hours. Absorption of hydrogen was exceedingly slow, only 300 c.c. being taken up in this time. The reaction was stopped at this point, the catalyst removed by filtration and the solvents evaporated from the filtrate by distillation under diminished pressure. The residue was divided into non-basic and basic fractions by dissolving it in ether and extracting the ethereal solution with dilute hydrochloric acid. The acid solution was then made alkaline and again extracted with ether. The bulk of the material was contained in the non-basic fraction.

Evaporation/

Evaporation of the ether from the basic fraction yielded only a trace of material which, although it apparently reacted with hydrochloride, only yielded an oily product with this acid. It seems clear from this result that the absorption of hydrogen which occurred during this experiment was due largely to the slow hydrogenation of the benzene ring.

Reduction of the cyano group with sodium and alcohol was excluded owing to the presence of the carbethoxy group in the molecule, which would, of course, undergo simultaneous reduction. It was thought, however, that reduction by this method might be carried out with the free cyano acid, if this could be obtained. An attempt was accordingly made to hydrolyse the ester, using, in this case, the ethoxymethyl compounds. 5 g. were dissolved in 10 c.c. of ether and the solution mixed with a solution of 2 g. of sodium hydroxide in 20 c.c. of water. The mixture was frequently shaken in order to maintain it as long as possible in the form of an emulsion. After 48 hours it was extracted with ether to remove non-acidic material and the aqueous fraction then acidified with dilute hydrochloric/

hydrochloric acid. This led to a copious evolution of carbon dioxide. Extraction of the solution with ether, moreover, failed to remove any acidic material. The bulk of the material was, in fact, contained in the non-acidic fraction. On attempting to distil this under diminished pressure, however, it underwent decomposition. There seems no doubt that, even under the mild conditions of hydrolysis which were employed the free acid lost carbon dioxide. Since this method of hydrolysis works quite satisfactorily in the case of phenyl-cyanoacetic ester it is clear that the presence of the ethoxymethyl group greatly diminishes the stability of the molecule.

In order to test whether the method of Harvey and Robson (J. Chem. Soc., 1938, 100) was applicable to cyanides, 2 g. of phenylethoxymethyl-cyanoacetic ester were dissolved in 40 c.c. of pyridine in a pressure bottle and the solution saturated with hydrogen sulphide at 0°. The bottle was then tightly closed and heated at 100° for 24 hours, when the solution was of a reddish-brown colour. The pyridine was now removed by distillation under diminished pressure, last

traces/

traces being removed by repeatedly adding alcohol to the residue and again distilling it off. The brown residual oil was dissolved in ether and extracted three times with dilute hydrochloric acid. This, however, removed no basic material from the product. The bulk of the material was in fact in the non-basic fraction. On attempting to purify this by distillation it passed over at an inconstant temperature (150-184/20 mm.) with decomposition, some hydrogen sulphide being at the same time evolved. Evidently some change was produced by the hydrogen sulphide although the nature of this is unknown.

The remaining methods of reduction examined were: heating with hydriodic acid and red phosphorus in glacial acetic acid; refluxing with phosphonium iodide in glacial acetic acid. These two methods were tested on benzylcyanide and, as might be expected, hydrolysis to phenylacetic acid occurred. Electrolytic reduction of phenylethoxymethylcyanoacetic ester using lead electrodes and a current density of 0.06 amp. led to the production of no basic material. Aluminium amalgam similarly gave no basic material.

Attempted Application of Stephen's Method to Phenylethoxymethylcyanoacetic Ester.

Preparation of anhydrous stannous chloride. In the first experiments the stannous chloride was prepared by the method originally described by Stephen (J. Chem. Soc., 1925, 1874). In view, however, of the necessity of working in the complete absence of water the improved method of Stephen (J. Chem. Soc., 1930, 2786) was subsequently used. To 40 g. of hydrated stannous chloride were added 40 g. of acetic anhydride. Much heat was developed. After half an hour the mixture was heated for a short time at 100°, cooled and filtered. The anhydrous stannous chloride was then thoroughly washed with dry ether and stored in a desiccator over sulphuric acid.

Application to phenylethoxymethylcyanoacetic ester. The method was first tested with benzonitrile, when a crystalline precipitate of the stannichloride of the aldimine was formed, exactly as described by Stephen. This readily underwent hydrolysis, giving/

giving an almost quantitative yield of benzaldehyde. The following experiment was then carried out with the above ester: 5 g. of anhydrous stannous chloride were covered with 30 c.c. of dry ether and dry hydrogen chloride was passed through the suspension until all the stannous chloride had dissolved. The liquid then usually formed two layers. 4 g. of phenylethoxymethylcyanoacetic ester were now added and the mixture shaken vigorously. No crystalline stannichloride separated in this case from the solution even when it was kept for several days. The experiment was therefore repeated, using the modifications of King and Robinson (J. Chem. Soc., 1933, 273) and King (J. Chem. Soc., 1936, 35) which consisted in saturating the ether at 0° and thus preventing the formation of two layers, heating the mixture after addition of the cyano compound, and then re-saturating with hydrogen chloride, but no better result was achieved. The method was also found to fail with ethyl phenylcyanoacetate and phenyl-malononitrile.

Attempted/

Attempted Conversion of Cyano into Amide Group.

Before the preparation of phenylethoxymethylmalonic acid by the method to be described below, an attempt was made to prepare this acid from phenylethoxymethylcyanoacetic ester through the ester of the half amide.

Partial hydrolysis of phenylcyanoacetic ester. The method was first tested on phenylcyanoacetic ester, 5 g. of which were dissolved in 15 g. of concentrated sulphuric acid and the solution stored in the refrigerator for 60 hours. The brown liquid was then poured on to crushed ice, when a solid separated. This was filtered and washed and recrystallised from acetone. Analysis indicated that the substance, which was obtained in practically theoretical yield, was phenylamidoacetic ester.

Analysis:

4.752 mg. gave 11.090 mg. CO_2; 2.760 mg. H_2O

5.212 mg. gave 0.300 c.c. N_2 at 747/15.5°C.

Found: C = 63.65; H = 6.50; N = 6.69%

$C_{11}H_{13}O_3N$ requires C = 63.70; H = 6.27; N = 6.76%

The/

The substance melted at 143º although Wislicenus and Goldstein (Ber., 1896, 29, 2602), who obtained it by heating phenylmalonic ester with excess of alcoholic ammonia at 100°, state that it melts at 152°.

Application to phenylethoxymethylcyanoacetic ester. When the above process was applied to this ester, the product failed to crystallise. It was therefore extracted with ether. On evaporation of the solvent a semi-solid mass was obtained which could not be crystallised. Nor could a crystalline acid be obtained from it after further hydrolysis. In view of the ease, as indicated by subsequent experiments, with which the ethoxy group can be removed from molecules of this type, there seems little doubt that a process of this nature occurred under the influence of the sulphuric acid.

Experiments/

Experiments on the Reduction of Phenylformyl Acetic Ester.

Preparation of phenylformylacetic ester. To 300 c.c. of ether containing 11.5 g. of sodium in the form of wire was added drop by drop a mixture of 82 g. of ethylphenylacetate and 45 g. of ethyl formate. The temperature was regulated partly by the rate of addition of the mixture and partly by cooling in ice water. After standing for about 12 hours, the brown ethereal solution was extracted with water, and the aqueous extract acidified with dilute sulphuric acid and extracted with ether. After drying over sodium sulphate the ether was evaporated when the residual oil was submitted to fractional distillation, the fraction boiling between 120-130°/10-11 mm. being used in subsequent experiments.

Benzoate of phenylhydroxymethylene acetic ester. McKenzie and Wood (J. Chem. Soc., 1919, 115, 828) have demonstrated that it is practically impossible to reduce phenylformylacetic ester. It was thought, however/

however, that such reduction might succeed if the molecule were stabilised in the hydroxymethylene form. The benzoate was therefore prepared by Wislicenus' method (Annalen, 1896, 291, 148). To a mixture of 180 c.c. of water and 150 c.c. of 20% sodium hydroxide were added 30 g. of phenylformylacetic ester and, in small portions at a time with cooling and shaking, 30 g. of benzoyl chloride. After standing overnight the solution had become acid; hence more alkali was added. The benzoate, which had separated in solid form was filtered, dried on a porous plate and recrystallised from alcohol, m.p. 87-88°.

Two methods of reduction of this benzoate were examined. In the first, 5 g. of the substance were shaken in the hydrogenation apparatus with 0.1 g. of Adam's platinum catalyst, using glacial acetic acid as solvent. No appreciable absorption of hydrogen, beyond that necessary to reduce the catalyst, occurred in 5 hours. The experiment was consequently stopped and the benzoate recovered unchanged from the reaction mixture.

In the second method, aluminium amalgam was used as reducing agent. 200 g. of thin aluminium foil were cut into strips about 6" x 1", loosely folded/

folded, covered with a 10% solution of sodium hydroxide, and warmed until a vigorous evolution of hydrogen had taken place for a few minutes. The foil was then thoroughly washed with water and finally, with alcohol. It was then left in contact with a 2% solution of mercuric chloride for several minutes, again washed with water, alcohol, and, finally, ether. To a flask containing 50 g. of the moist aluminium amalgam were added a solution of 10 g. of the benzoate of phenylhydroxymethylene acetic ester in 200 c.c. of moist ether. An immediate development of heat occurred. The flask was shaken from time to time and finally heated, under reflux, on a water bath for about an hour. The ether was filtered from the muddy solid, the latter extracted repeatedly with ether, and the combined extracts dried over sodium sulphate. Evaporation of the ether left only a minute amount of oil which was too small in amount for identification. This result is similar to that obtained by McKenzie and Wood (J. Chem. Soc., 1919, 115,828) in their attempt to effect the direct reduction of phenylformylacetic ester by this method.

Ethyl/

Ethyl ether of phenylhydroxymethylene acetic acid.

$$C_6H_5.C(=CH.OC_2H_5).COOC_2H_5$$

There was a possibility that the difficulties experienced in the reduction of the above compounds were due to the accumulation of negative groups in the vicinity of the double bond. The ethyl ether, represented by the above formula, was therefore prepared by a method for the ethylation of hydroxymethylene compounds recently published by v. Auwers (Ber., 1938, 71, 2082). To 28 g. of phenylformyl acetic ester were added 8 g. of anhydrous sodium carbonate and a solution of 35 g. of ethyliodide in 50 c.c. of dry methylethyl ketone, and the mixture refluxed on the water bath for 24 hours. The sodium iodide was then precipitated by the addition of ether, the solution filtered, and the solvents removed by distillation. The residual oil was then purified by fractional distillation. After three distillations the bulk of the material boiled at 160.5-162°/12 mm. This was the required ether.

Analysis/

Analysis:

4.164 mg. gave 10.755 mg. CO_2 ; 2.740 mg. H_2O.

Found: C = 70.44%; H = 7.36%.

$C_{13}H_{16}O_3$ requires C = 70.90%; H = 7.27%.

The catalytic hydrogenation of this ether was attempted by the method employed with the benzoate, but no hydrogen was absorbed either when alcohol or glacial acetic acid was used as solvent.

Action of sodium on ethyl-phenylacetate.

By the action of sodium and ethylformate on phenylacetic ester a formyl group can, as described at the beginning of this section, be introduced into the phenylacetic ester molecule. The following experiment, which was actually an attempt to introduce an ethoxymethyl group into the molecule is recorded because it illustrates the behaviour of phenylacetic ester towards sodium. To a flask containing a suspension of 4.6 g. of powdered sodium in 150 c.c. of ether were added slowly 33 g. of phenylacetic ester. Evolution of hydrogen occurred and heat was developed. When the reaction ceased the brown solution was cooled in ice and 22 g. of chloromethylethyl ether were slowly/

slowly added to it. The mixture was then refluxed for a short time on the water bath. The sodium chloride which had separated was then dissolved by the addition of water, the ethereal solution separated, dried over sodium sulphate, and the solvent removed. The residual oil was distilled at 12 mm. pressure. A small amount passed over between the temperatures of 80° and 120°, but the bulk of the material remained in the flask as a viscous mass. There seems no doubt that, unless there is another ester present with which it can condense, as in the preparation of phenylformyl-acetic ester, phenylacetic ester condenses with itself in the presence of sodium with the formation of one or more substances of high molecular weight.

Preparation of tropic acid ethyl ether.

$$C_6H_5.\underset{H}{\overset{CH_2.O.C_2H_5}{C}}.COOH$$

Preparation of phenylmalonic ester. (Wislicenus, Annalen, 1888, 246, 315; Ber., 1894, 27, 1092). Alcohol-free sodium ethoxide was prepared by dissolving 12 g. of sodium in alcohol (200 c.c.), passing/

passing a current of hydrogen through the solution, distilling off the alcohol and then heating the residue, still in a current of hydrogen, at a temperature of 200° for about 2 hours. To the sodium ethoxide so prepared were added 250 c.c. of dry ether and 73 g. of ethyl oxalate. Phenylacetic ester (82 g.) was then added slowly from a dropping funnel. The sodium ethoxide gradually went into solution and, within an hour of completing the addition, the contents of the flask set to a solid mass. The solid, which was the sodium derivative of oxalylphenylacetic ester, was filtered and washed thoroughly with ether. It was then dissolved in water, decomposed with dilute sulphuric acid, and the oxalylphenyl acetic ester extracted with ether. After drying over sodium sulphate and removing the ether the residual liquid was heated under diminished pressure. With the temperature of the bath between 160 and 170° an evolution of carbon monoxide, as indicated by a rise in the pressure, occurred. Further heating was interrupted at this point and the temperature kept below 170° until the decomposition of the

oxalyl/

oxalyl compound was complete. The temperature of the bath was then raised, when 96 g. (81% of theoretical) of phenylmalonic ester distilled over at 168°/20 mm.

Phenylethoxymethylmalonic ester. $C_6H_5.C(CH_2.O.C_2H_5)(COOC_2H_5)(COOC_2H_5)$

To 6 g. of powdered sodium suspended in 200 c.c. of ether were slowly added 59 g. of phenylmalonic ester. A reaction occurred with the evolution of hydrogen and solid sodiophenylmalonic ester soon began to separate as a white solid. When all the sodium had disappeared the flask was cooled in ice and 35 g. of chloromethylethyl ether dissolved in an equal volume of ether were slowly added to its contents. A vigorous reaction took place, the solid going into solution and sodium chloride separating in its place. When the contents of the flask were found to be acid to litmus, water was added and, after vigorous shaking, the ether layer separated. This was washed with water, dried over sodium sulphate, and/

and the ether removed. The residual oil was then submitted to fractional distillation. Two main fractions, b.p. 129-139°/1-2 mm. and 139-151°/1-2 mm. were first collected. After repeated fractionation of these phenylethoxymethylmalonic ester was obtained as a colourless liquid, b.p. 150-151°/1-2 mm. Yield 45 g.

Analysis:

3.258 mg. gave 7.780 mg. CO_2 and 2.215 mg. H_2O

Found: C = 65.13%; H = 7.61%.

$C_{16}H_{22}O_5$ requires C 65.36%; H = 7.48%.

Isolation of atropic acid by hydrolysis of phenylethoxymethylmalonic ester. In a preliminary experiment carried out with the object of finding the best conditions for the hydrolysis of the above ester, 1 g. of the ester was added to a solution of 0.156 g. (2 atoms) of sodium in 10 c.c. of alcohol to which 1 c.c. of water had been added. The solution was kept warm for about an hour, during which time some/

some solid slowly separated. This was filtered and was found to consist mainly of sodium carbonate. Evidently decarboxylation of the acid was occurring under these conditions. Two more atoms of sodium in the form of sodium ethoxide were therefore added to the filtrate and the liquid was again warmed for half an hour. No more solid separated. The alcohol was evaporated on the water bath, the residue dissolved in water and extracted with ether to remove non-acidic material. It was then acidified with dilute sulphuric acid, which caused an evolution of carbon dioxide, and again extracted with ether. The latter extract was dried over sodium sulphate and the ether evaporated, when an oily residue was obtained which partly crystallised. The crystals were drained from the oil on a porous plate. They were then dissolved in alcohol and decolorised with a little animal charcoal. On addition of water to the alcoholic solution, crystalline material separated. This was re-crystallised from aqueous methyl alcohol, when it formed plates m.p. 106°. This was recognised to be the melting point of atropic acid, but as no authentic specimen of the acid was available with/

with which to compare it, it was analysed. This confirmed the fact that some atropic acid had been formed by the hydrolysis of phenylethoxymethylmalonic ester under the above conditions.

Analysis:

5.154 mg. gave 13.750 mg. CO_2 and 2.600 mg. H_2O.

Found: C = 72.76; H = 5.65%.

$C_9H_8O_2$ requires C = 73.00; H = 5.40%.

Preparation of phenylethoxymethylmalonic acid.

After some further preliminary experiments this acid was obtained as follows. 4.5 g. (4 atomic proportions) of sodium were dissolved in 60 c.c. of alcohol containing 5 c.c. of water. To the hot solution were then added a further 30 c.c. of cold alcohol and 5 c.c. of water. This was followed immediately by the addition of 14.5 g. of phenylethoxymethylmalonic ester. The mixture was then allowed to stand overnight without further heating. During this time radiating clusters of crystals together with opaque granular material had separated. This was filtered, dissolved in water/

water and acidified with dilute sulphuric acid. A considerable effervescence occurred, indicating the presence of a moderate amount of sodium carbonate, and, after a few minutes, crystalline needles separated from the solution. This was filtered (Yield 3.9 g.) and was pure phenylethoxymethyl-malonic acid. It is not very soluble in the ordinary organic solvents in the cold. Hence, in order to avoid heating it, a small portion was recrystallised for analysis by dissolving it in ether, in which it is moderately soluble, and adding petroleum ether to the solution. The crystals so obtained melted with effervescence at 123°. With rapid heating the decomposition point is higher.

Analysis:

4.665 mg. gave 11.945 mg. CO_2 and 2.950 mg. H_2O.

Found: C = 60.97; H = 6.18%.

$C_{12}H_{14}O_5$ requires C = 60.50; H = 5.88%.

Preparation/

Preparation of tropic acid ethyl ether.

$$C_6H_5.\ \underset{\underset{H}{|}}{\overset{\overset{CH_2.O.C_2H_5}{|}}{C}}.COOH$$

The above dicarboxylic acid was heated in an oil bath until it melted. Evolution of carbon dioxide took place and the heating was continued at about 125° until this ceased. The liquid reaction product was dissolved in petroleum ether, filtered from a little unchanged dicarboxylic acid, and the petroleum ether evaporated. A colourless oil was left which slowly solidified to a hard crystalline mass. For further work it was used in this form, but a small portion was crystallised for analysis by dissolving it in alcohol and slowly adding water to the solution. The substance tends to separate first as an oil and then forms clusters of radiating needles. It can also be recrystallised from petroleum ether, from which it slowly separates as a crystalline crust on the walls of the flask. This method of crystallisation is, however, wasteful owing to the moderate solubility of the substance in this solvent. It melts at 46°, but the melt is not/

not quite clear. This is attributed to the presence in the tropic acid ethyl ether of a little atropic acid, and analysis appears to confirm this.

Analysis:

4.665 mg. gave 11.945 mg. CO_2 and 2.950 mg. H_2O.

Found: C = 69.83; H = 7.08%.

$C_{11}H_{14}O_3$ requires C = 68.04; H = 7.22%.

Isolation of tropic acid ethyl ether from the hydrolysis product of phenylethoxymethylmalonic ester. After the hydrolysis of this ester, in the experiment described above, the alcoholic mother liquors obtained after filtration of the sodium phenylethoxymethylmalonate were evaporated to dryness under diminished pressure and the residue dissolved in water. The solution so obtained was extracted with ether, acidified with dilute sulphuric acid, which caused the precipitation of an oil, and again extracted with ether. The latter extract, after drying over sodium sulphate and removing the solvent, yielded a faintly yellow oil. This was extracted repeatedly by decantation with warm petroleum ether, finally leaving/

leaving a small insoluble residue of semi-solid material, which was not examined further. The combined extracts were then warmed with a little animal charcoal, filtered, and the colourless solution evaporated to dryness, when a colourless oil was obtained which slowly solidified to a hard crystalline mass. This melted at 46° and proved to be identical with the tropic acid ethyl ether obtained in the preceding experiment. Yield 3.2 g.

Preparation of ethyl ester of tropic acid ethyl ether.

10 g. of the above acid were dissolved in alcohol and the solution saturated with dry hydrogen chloride. After some hours the solvent was removed by distillation under diminished pressure. The residue was dissolved in ether, the solution so obtained washed with water, dried over sodium sulphate, and the ether evaporated. The residue was then fractionally distilled. After two fractionations the ethyl ester was obtained as a colourless liquid, b.p. 100°/1-2 mm. Yield 9 g.

Analysis/

Analysis:

6.856 mg. gave 17.845 mg. CO_2 and 4.940 mg. H_2O.

Found: C = 70.98%; H = 8.06%.

$C_{13}H_{18}O_3$ requires C = 70.27%; H = 8.11%.

Action of sodium and chloromethylethylether on ethyl ether of tropic ester. To a suspension of 0.95 g. of powdered sodium in 20 c.c. of ether were slowly added 9 g. of the ethyl ether of tropic ester. Hydrogen was evolved and the solution became warm. At the end of the reaction the slight application of heat was necessary to complete the solution of the final traces of sodium. The solution became brown but no separation of a sodium salt occurred. The flask was now cooled in ice, when 6 g. of chloromethylethyl ether dissolved in an equal volume of ether were added. A vigorous reaction took place with the separation of sodium chloride. The mixture was shaken with water, the ether separated, dried over sodium sulphate, and evaporated. A viscous syrup remained. An attempt was made to distil this in a high vacuum, but only a small portion, which boiled constantly at 200°/1 mm./

mm., passed over, the remainder setting on cooling to a glass-like solid. In order to gain an approximate idea of the composition of the distillate it was analysed.

Analysis:

5.308 mg. gave 14.220 mg. CO_2 and 3.525 mg. H_2O.

Found: C = 73.06%; H = 7.43%.

$C_{24}H_{29}O_5$ requires C = 72.54%; H = 7.30%.